Global burden of Shigella infections

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Global burden of *Shigella* infections: implications for vaccine development and implementation of control strategies

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Few studies provide data on the global morbidity and mortality caused by infection with *Shigella* spp.; such estimates are needed, however, to plan strategies of prevention and treatment. Here we report the results of a review of the literature published between 1966 and 1997 on *Shigella* infection. The data obtained permit calculation of the number of cases of *Shigella* infection and the associated mortality occurring worldwide each year, by age, and (as a proxy for disease severity) by clinical category, i.e. mild cases remaining at home, moderate cases requiring outpatient care, and severe cases demanding hospitalization. A sensitivity analysis was performed to estimate the high and low range of morbid and fatal cases in each category. Finally, the frequency distribution of *Shigella* infection, by serogroup and serotype and by region of the world, was determined.

The annual number of *Shigella* episodes throughout the world was estimated to be 164.7 million, of which 163.2 million were in developing countries (with 1.1 million deaths) and 1.5 million in industrialized countries. A total of 69% of all episodes and 61% of all deaths attributable to shigellosis involved children under 5 years of age. The median percentages of isolates of *S. flexneri, S. sonnei, S. boydii*, and *S. dysenteriae* were, respectively, 60%, 15%, 6%, and 6% (30% of *S. dysenteriae* cases were type 1) in developing countries; and 16%, 77%, 2%, and 1% in industrialized countries. In developing countries, the predominant serotype of *S. flexneri* is 2a, followed by 1b, 3a, 4a, and 6. In industrialized countries, most isolates are *S. flexneri* 2a or other unspecified type 2 strains.

Shigellosis, which continues to have an important global impact, cannot be adequately controlled with the existing prevention and treatment measures. Innovative strategies, including development of vaccines against the most common serotypes, could provide substantial benefits.

Voir page xx le résumé en français. En la pagina xx figura un resumen en español.

Introduction

A convergence of events and opportunities makes this a propitious moment to estimate the magnitude of the global burden of disease and death caused by *Shigella*. Several recent trends underscore the limitations of modern medical and public health efforts in controlling this global threat, the consequences of which are most devastating in the developing world. Since the 1970s, the vigorous use of oral rehydration therapy in developing countries has contributed significantly to reductions in mortality from diarrhoeal dehydration (*1–4*). In contrast, this intervention provides little benefit to patients with dysentery caused by invasive bacterial enteropathogens such as *Shigella*. As a result, the relative importance of dysentery as a clinical problem in developing countries has increased (*5*). At a diarrhoeal disease centre in Bangladesh, between 1975 and 1985, deaths attributed to acute or chronic dysentery among 1–4-year-old children outnumbered the deaths attributed to acute or chronic watery diarrhoea by a factor ranging from 2.1 to 7.8 (*6*).

Over the last 50 years, *Shigella* has demonstrated extraordinary prowess in acquiring plasmid-encoded resistance to the antimicrobial drugs that previously constituted first-line therapy. Sulfonamides, tetracycline, ampicillin and trimethoprim–sulfamethoxazole initially appeared as highly efficacious drugs, only to become impotent in the face of emerging

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resistance (*7*). In the 1990s, few reliable options exist to treat multiresistant *Shigella* infections, particularly in developing countries where cost and practicality are paramount considerations.

Since the late 1960s, pandemic waves of Shiga (*S. dysenteriae* type 1) dysentery have appeared in Central America, south and south-east Asia and sub-Saharan Africa, often affecting populations in areas of political upheaval and natural disaster (*8–10*). When pandemic *S. dysenteriae* type 1 strains invade these vulnerable populations, the attack rates are high and dysentery often becomes a leading cause of death (*10*).

Shigella infections also occur in industrialized countries (*11, 12*). Groups that exhibit suboptimal levels of hygiene, such as toddlers and preschool-age children in day-care centres (*13*) or persons residing in custodial institutions (*14*), can experience outbreaks of shigellosis. In some urban areas, endemic transmission is sustained. *Shigella* spp. are common etiological agents of diarrhoea among travellers to less developed regions of the world, and tend to produce a more disabling illness than enterotoxigenic *Escherichia coli* (*15*), the leading cause of travellers' diarrhoea syndrome.

The intersection of *Shigella* infections and the human immunodeficiency virus (HIV) epidemic has had serious consequences. Both chronic diarrhoea and dysentery are common among persons infected with HIV (*16, 17*); in studies of chronic diarrhoea and dysentery in developing regions, *Shigella* has sometimes been the most common pathogen identified (*17, 18*). In industrialized countries, *Shigella* spp. are often identified in homosexual men with colitis or proctocolitis (*19, 20*). Although it is not known whether the risk of acquiring shigellosis is enhanced by concomitant HIV infection (*21*), it appears that HIV-associated immunodeficiency leads to more severe clinical manifestations of *Shigella* infection. Patients with HIV infection may develop persistent or recurrent intestinal *Shigella* infections, even in the presence of adequate antimicrobial therapy. They also face an increased risk of *Shigella* bacteraemia, which can be recurrent, severe or even fatal (*22–25*).

Despite the continuing challenge posed by *Shigella*, there is room for optimism as advances in biotechnology have enabled the development of a new generation of candidate vaccines that shows great promise for the prevention of *Shigella* disease (*26–28*). The state of progress in the development and testing of the new *Shigella* vaccines was reviewed at a meeting convened by WHO (*29*). As with any new vaccine, assessments of cost-effectiveness and other economic analyses help guide both development and implementation. A prerequisite to such economic analyses is a reliable estimate of *Shigella* disease burden, including information on the relative occurrence of the various serogroups and serotypes in different geographical areas (*30*). In view of the background summarized above, we have quantified the global burden of *Shigella* infections in both developing and industrialized countries.

Materials and methods

The initial studies selected for this review were identified by a computer search of the multilingual scientific literature published between 1966 and 1997. A set of 9240 articles, derived using the keywords *Shigella*, dysentery, bacillary, and shigellosis, was linked with a set of 902 934 articles obtained using the following keywords that dealt with disease burden: incidence, prevalence, public health, death rate, mortality, surveillance, burden, suffering, distribution, area, location, country, and permutations of the root words: epidemiol-, monitor-, geograph-. The resulting cross-linked set contained 1530 articles which were culled to select 305 articles relevant to the stated goal of the search (available upon request). Additional (mainly pre-1966) references were found from citations listed in these 305 articles and from the archives of the authors and experts in the field.

An algorithm was created to estimate the number of cases of *Shigella* infection that occur worldwide each year. In a preliminary step, the world's population was divided into ten strata based on age (0–11 months, 1–4 years, 5–14 years, 15–59 years, and >60 years); countries were designated as developing or industrialized according to United Nations criteria (*31*). Published rates of diarrhoeal incidence for each of the ten strata were used to estimate the diarrhoeal disease burden. The proportion of diarrhoeal episodes attributable to *Shigella* depends on the severity of the patient's illness. We expected that this correlation would increase as the percentage of *Shigella* infections increases as sampling progresses from cases of diarrhoea detected by household surveillance to those found among outpatients in treatment centres to those that were admitted to hospital with diarrhoeal illness (*32*). Accordingly, the total diarrhoeal disease burden was subdivided into three settings: estimates of mild cases remaining at home; more severe cases requiring clinical care at a treatment centre but not needing hospitalization; and cases demanding hospitalization.

The proportion of diarrhoea episodes in each stratum that can be attributed to shigellosis was estimated by analysing studies that met the following criteria: the percentage of diarrhoea cases that were microbiologically confirmed as due to *Shigella* using conventional bacteriological culture methods was reported for the specified age group (*33*); the sample included at least 100 cases of diarrhoea, i.e. there was a >99% probability of detecting at least one case if the true prevalence was 5%; surveillance was conducted for at least one year; and for household studies, there was at least biweekly surveillance for diarrhoea. When multiple studies were conducted in one country during overlapping time spans and in similar settings, a median value for shigellosis cases was derived. An overall median percent shigellosis was then calculated for each stratum and multiplied by the total number of diarrhoeal cases in the stratum to derive the number of *Shigella* cases in each stratum. These numbers of *Shigella* cases were summed to give an

overall burden of *Shigella* morbidity. Published case-fatality rates for persons hospitalized with *Shigella* infection were used to calculate age-specific rates of *Shigella*-associated mortality.

To estimate the burden of *Shigella* infection by serogroup and serotype, we analysed studies that met the following criteria: 1) systematic microbiological surveillance had been performed for at least one year, using recognized laboratory techniques (*33*); 2) with the exception of one community cohort study in Guatemala (*34*), the clinical venue was either a treatment setting or an inpatient ward of a hospital, thereby capturing serotypes associated with a more severe spectrum of clinical illness; and 3) data were collected after 1979. Countries were grouped by region according to published criteria (*31*) and a median frequency distribution by region was calculated.

Results

Endemic disease among under-5-year-olds in developing countries

Population statistics. Of the total world population of ca. 5700 million inhabitants in 1995, nearly 4600 million people were estimated to reside in non-industrialized countries (*35*), including 125 million infants aged 0–11 months and 450 million children aged 1–4 years.

Diarrhoeal incidence. The estimates of Bern et al. (*36*) were used to gauge the number of episodes of diarrhoea per year among under-1-year-old infants and in children aged 1–4 years. These estimates are based on a review of 22 longitudinal community studies of stable populations in 12 developing countries in Asia, Latin America and Africa where active surveillance for diarrhoea was conducted between 1981 and 1987 using at least biweekly home monitoring for a minimum of 1 year. The median incidences were 3.9 episodes per child per year for 0–11-month-olds and 2.1 episodes per child per year for children aged 1–4 years.

Total number of diarrhoeal episodes. By multiplying the population of children by the incidence of diarrhoea in each age group, we calculated the total number of diarrhoeal episodes to be 487. 5 million for 0–11-month-old infants and 945 million for children aged 1–4 years (Table 1).

Number of diarrhoeal episodes in the three study settings. Data collected in the mid-1980s in a poor peri-urban community in Santiago, Chile, revealed that among 0–11-month-olds, 88.2% of episodes of diarrhoea were mild cases that did not seek health care but were detected by active household surveillance, 10.3% were outpatients at an ambulatory treatment centre, and 1.5% required hospital admission (*32* and R. Lagos, unpublished data, 1989). Among 1–4-year-olds, 91.9% of episodes were domiciliary, 7.9% went to treatment centres, and 0.2% were admitted to hospitals. These estimates were confirmed in another part of Chile using data from 1995 and 1996 (R. Lagos, P. Abrego, M.M. Levine, unpublished data, 1996). Since we did not have similar data available from other areas in nonindustrialized countries, the Chilean data were extrapolated to estimate the overall number of diarrhoea cases in each age group who stayed at home, were seen at a treatment centre, or were admitted to hospital (Table 1).

Table 1. **Estimating the annual number of episodes of diarrhoea among 0–4-year-old children living in developing countries, by age group, in each of three settings**

	Age group		
	0–11 months	**1–4 years**	**Total (0–4 years)**
Total population	125 000 000	450 000 000	575 000 000
No. of diarrhoeal episodes per child per year [a]	3.9	2.1	NA[b]
Total: all diarrhoeal episodes	487 500 000	945 000 000	1 432 500 000
No. of episodes at home	429 975 000 (91.9)	868 455 000 (88.2)[c]	1298 430 000
No. of episodes in outpatients	50 212 500 (10.3)[b]	74 655 000 (7.9)	124 867 500
No. of cases hospitalized	7 312 500 (1.5)[b]	1 890 000 (0.2)	9 202 500

[a] From ref. *36*.

[b] NA: not applicable.

[c] Figures in parentheses are percentages of total diarrhoeal episodes (from ref. *32*).

Percentage of diarrhoea due to* Shigella *in the three study settings. Studies conducted in a developing country that met the inclusion criteria were analysed to determine the percentage of diarrhoea cases due to *Shigella* among children aged 0–11 months and 1–4 years.

- 0–11-Month-old infants. As shown in Table 2, the median frequency of *Shigella* isolation from diarrhoea cases in this age group was 3.2% (range, 2.2–5.3%) for those treated at home (results of six studies: *32, 37–41*), 6.3% (range, 1.6–30.0%) for those in treatment centres (eight studies: *32, 42–47*), and 6.5% (range, 3.6–11.0%) for those treated in hospital (four studies: *32, 48–50*).
- 1–4-Year-old children. As shown in Table 3, the median percentage of diarrhoeal episodes from which *Shigella* was cultured was 9.1% (range, 5.5–18.7%) in household cases (four studies: *32, 40, 41, 51*), 22.0% (range, 13.0–39.0%) for those in treatment centres (six studies: *32, 42–44, 46*), and 16.5% (range, 8.0–32.0%) for those treated in hospital (four studies: *32, 48–50*).

Burden of shigellosis in under-5-year-olds in the three study settings. The total number of cases of diarrhoea attributable to *Shigella* in each of the three settings was calculated for the 0–11-month and 1–4-year age groups by multiplying the percentage of episodes from which *Shigella* was identified by the

Table 2. **Proportion of diarrhoeal episodes in which *Shigella* was detected among infants aged 0–11 months in three surveillance settings**

Domicile				Outpatient treatment centre				Hospital			
Country	Years	Setting	No. of *Shigella* episodes/ total episodes	Country	Years	Setting	No. of *Shigella* episodes/ total episodes	Country	Years	Setting	No. of *Shigella* episodes/ total episodes
Chile(ref. *32*)	1986–89	Urban	8/171 (4.7)[a]	Chile (ref. *32*)	1986–89	Urban	30/605 (5.0)	Chile (ref. *32*)	1986–89	Urban	17/215 (8.0)
Mexico (ref. *37*)	1985–87	Rural	7/314 (2.2)	Nigeria (ref. *43*)	1984–85	Rural	43/391 (11.0)	India (ref. *48*)	1985–88	Urban	22/210 (11.0)
Peru (ref. *38*)	1982–84	Urban	19/825 (2.3)	Bangladesh (ref. *46*)	1975–84	Rural	49/162 (30.0)	Philippines (ref. *49*)	1983–84	Urban	63/1247 (5.0)
Mexico (ref. *39*)	1982–83	Rural	9/170 (5.3)	Bangladesh (ref. *42*)	1983–84	Rural	14/240 (6.0)	Islamic Republic of Iran (ref. *50*)	1986–87	Urban	19/527 (3.6)
Thailand (ref. *40*)	1988–89	Urban	4/164 (2.4)	Bangladesh (ref. *44*)	1979–80	Urban	57/876 (6.5)				
Egypt (ref. *41*)	1981–83	Rural	8/207 (3.9)	Brazil (ref. *45*)	1985–86	Urban	25/500 (5.0)				
				Somalia (ref. *47*)	1983–84	Urban	12/745 (1.6)				
				China, India, Mexico, Pakistan (ref. *98*)	1982–85	Urban	137/1809 (7.6)				
Median %			**3.2**				**6.3**				**6.5**

[a] Figures in parentheses are percentages.

Table 3. **Proportion of diarrhoeal episodes in which *Shigella* was detected among children aged 1–4 years in three surveillance settings**

Domicile				Outpatient treatment centre				Hospital			
Country	Years	Setting	No. of *Shigella* episodes/ total episodes	Country	Years	Setting	No. of *Shigella* episodes/ total episodes	Country	Years	Setting	No. of *Shigella* episodes/ total episodes
Chile (ref. *32*)	1986–89	Urban	106/966 (11.0)[a]	Chile (ref. *32*)	1986–89	Urban	138/1050 (13.0)	Chile(ref. *32*)	1986-89	Urban	21/65 (32.0)
Bangladesh (ref.*51*)	1978–79	Rural	68/364 (18.7)	Nigeria (ref. *43*)	1984–85	Rural	121/826 (15.0)	Philippines (ref. *49*)	1983–84	Urban	110/1152 (10.0)
Thailand (ref. *40*)	1988–89	Urban	13/181 (7.2)	Bangladesh (ref. *46*)[b]	1975–84	Rural	285/740 (39.0)	India (ref. *48*)	1985–88	Urban	170/740 (23.0)
Egypt (ref. *41*)	1981–83	Rural	35/636 (5.5)	Bangladesh (ref. *42*)	1983–84	Rural	73/523 (14.0)	Islamic Republic of Iran (ref. *50*)	1986–87	Urban	13/170 (8.0)
				Bangladesh (ref. *44*)[b]	1979–80	Urban	379/1310 (29.0)				
				China, India, Mexico, Pakistan (ref. *98*)[b]	1982–85	Urban	230/1004 (29.0)				
Median %			**9.1**				**22.0**				**16.5**

[a] Figures in parentheses are percentages.

[b] Children evaluated were 1–3 years of age.

number of diarrhoea cases seen in each setting, as summarized in Table 4. In this manner, it was estimated that a total of 113 163 260 episodes of shigellosis occurred each year among under-5-year-olds in the developing world.

Endemic disease among older children and adults living in developing countries

Population statistics. Three age strata were used in estimating the *Shigella* disease burden among older children and adults: 5–14 years (school-age children), 15–59 years (adults), and ⩾60 years (elderly). The population of these age groups in developing countries is 1 010 985 000, 2 646 608 000 and 329 450 000, respectively, i.e. a total of 3 987 043 000 (*35*).

Incidence and burden of diarrhoea. Only a single household-based epidemiological study of adults could be identified which fulfilled our criteria; even this study, which was conducted in southern China, was suboptimal in that surveillance was conducted only once per month. In this Chinese study, for the age groups 5–14 years, 15–59 years and ⩾60 years, the average incidence of diarrhoea was 0.65, 0.50, and 0.69 episodes per person per year,

Table 4. **Annual number of episodes of *Shigella* diarrhoea among 0–4 year-olds living in developing countries**

Age group	Setting			Total episodes of *Shigella* diarrhoea
	Domicile	Outpatient	Inpatient	
0–11 months				
Annual number of diarrhoea episodes	429 975 000	50 212 500	7 312 500	
% episodes with *Shigella* spp.	3.2	6.3	6.5	
Total *Shigella* episodes	13 759 200	3 163 390	475 315	17 397 905
1–4 years				
Annual number of diarrhoea episodes	868 455 000	74 655 000	1 890 000	
% episodes infected with *Shigella* spp.	9.1	22.0	16.5	
Total *Shigella* episodes	79 029 405	16 424 100	311 850	95 765 355
Total *Shigella* episodes, 0–4 years	**92 788 605**	**19 587 490**	**787 165**	**113 163 260**

respectively (*52*). This suggests that the lower estimate of diarrhoeal incidence among over-5-year-olds is roughly 0.5 episodes per person per year, i.e. 50% of persons in this age group experience diarrhoea each year. We applied these rates to estimate the age-specific annual number of diarrhoeal episodes occurring in older children and adults in developing countries (Table 5).

Percentage of diarrhoeal illness reaching medical attention. Only one study was found that could be used to estimate the incidence of diarrhoea in adults that was of sufficient severity to prompt individuals to seek medical care. This study measured the number of cases of diarrhoea seen at health centres that serve 90% of people living in a community of 140 000 residents in a lower socio-economic suburb of Lima, Peru, and reported an

Table 5. **Annual numbers of diarrhoea episodes and of *Shigella* episodes among older children and adults living in developing countries**

	Age group			
	5–14 years	15–59 years	⩾60 years	Total
Population	1 010 985 000	2 646 608 000	329 450 000	3 987 043 000
No. of diarrhoeal episodes per person per year[a]	0.65	0.50	0.69	NA[b]
Total number of diarrhoeal episodes	657 140 250	1 323 304 000	227 320 500	2 207 764 750
Annual number of diarrhoeal episodes:				
Reaching a treatment facility[c]	13 142 805	26 466 080	4 546 410	44 155 295
Remaining in domicile	643 997 445	1 296 837 920	222 774 090	2 163 609 455
Estimated % of diarrhoeal episodes attributed to *Shigella:*				
Reaching a treatment facility[d]	13.5	15.6	18.5	NA
Remaining in domicile[e]	2.0	2.0	2.0	NA
Annual number of *Shigella* diarrhoea episodes:				
Reaching a treatment facility	1 774 280	4 128 710	841 085	6 744 075
Remaining in domicile	12 879 950	25 936 760	4 455 480	43 272 190
Total	**14 654 230**	**30 065 470**	**5 296 565**	**50 016 265**

[a] Ref. *52*.

[b] NA: not applicable.

[c] This calculation assumes that approximately 2% of diarrhoeal episodes reach a treatment facility, and is based on the observation that at least 50% of persons in this age group experience diarrhoea each year (ref. *52*) and 1.2% seek medical care (ref. *53*), i.e. approximately 0.012/0.50, or 2% of diarrhoeal episodes in developing countries require medical attention each year.

[d] From Table 6.

[e] The percentage is based on estimates from reference *54*.

annual rate of 11.8 episodes per 1000 population, i.e. 1.2% (*53*). Limitations of the study were that it lasted only 6 months (January to June), did not stratify by age after 15 years, and did not differentiate outpatient visits from hospitalizations. Thus, an overall estimate, without stratification for age or treatment setting, was made for the proportion of patients aged >5 years who sought medical care for their diarrhoeal illness, as follows: if 50% of persons in this age group experience diarrhoea each year (vide supra), and 1.2% seek medical care (*53*), approximately 0.012/0.50 (2%) of diarrhoeal episodes among school-aged children and adults living in developing countries require medical attention each year (Table 5).

***Percentage of diarrhoea that is attributable to* Shigella**. Table 6 summarizes the studies that report the percentage of diarrhoeal episodes associated with *Shigella* isolation in all types of treatment centres or hospitals for patients aged ⩾5 years. The median percentages for the age groups 5–14, 15–59, and ⩾60 years were estimated to be 13.5%, 15.6%, and 18.5%, respectively. No studies provide data to indicate what proportion of the remaining cases of diarrhoea that are mild (i.e. do not result in health care visits) might be attributable to *Shigella*, although some experts have estimated 8% (*54*). To maintain conservative estimates, we selected 2% as the value to use in further calculations (Table 5).

Total burden of shigellosis among older children and adults living in developing countries. The assumptions stated above permit a calculation of the total annual *Shigella* burden, i.e. cases remaining at home and those receiving medical attention among children aged ⩾5 years and adults living in developing countries. The burden was calculated by multiplying the number of patients with diarrhoea in each age stratum and clinical venue by the median proportion of episodes in each age stratum that is estimated to be caused by *Shigella*. Thus, the estimated annual number of cases of shigellosis among persons aged 5–14, 15–59, and ⩾60 years is 14 654 230, 30 065 470 and 5 296 565, respectively, i.e. a total of 50 016 265 (Table 5).

Total burden of shigellosis among persons living in developing countries. The estimated disease burden from shigellosis among adults and older children living in developing countries is roughly 50.0 million cases per year (Table 5). This compares with ca. 113.2 million cases for the age group <5 years (Table 4), and results in an estimated annual disease burden for all age groups living in developing countries of 163.2 million persons.

Cases of shigellosis in industrialized countries

The *Shigella* burden in industrialized countries was calculated using national surveillance data because there is a paucity of prospective longitudinal studies. Surveillance data are presented below from Australia, France, England and Wales, Israel, and USA. To obtain a more accurate estimate of disease incidence, a correction factor based on the rate of case ascertainment (completeness of reporting) was applied to the reported incidences, as described below.

***Shigella* in Australia.** *Shigella* isolations are reported to the Australian National Notifiable Diseases Surveillance System from all States and Territories, except New South Wales, where it was only reportable as a foodborne disease in two or more related cases or as gastroenteritis in an institutional

Table 6. **Percentage of diarrhoeal episodes that were evaluated in treatment centres and hospitals in which *Shigella* was isolated among patients aged ⩾5 years living in developing countries**

			No. of episodes in which *Shigella* was isolated in each assigned age stratum[a] (%)		
Country	**Year**	**Setting**	**5–14 years**	**15–59 years**	**⩾60 years**
Saudi Arabia (ref. *99*)	1987–89	Rural	NR[b]	18/71 (25.3)	NR
Bangladesh (ref. *46*)	1975–84	Rural	275/588 (46.8)	284/771 (36.8)	78/227 (34.4)
Bangladesh (ref. *42*)	1983–84	Rural	67/537 (12.5)	60/786 (7.6)	32/246 (13.0)
Bangladesh (ref. *44*)	1979–80	Urban	57/438 (13.0)	107/869 (12.3)	13/57 (22.8)
Thailand (ref. *100*)	1982–83	Rural	5/25 (20.0)	4/86 (4.7)	9/66 (13.6)
Thailand (ref. *101*)	1980–81	Urban	NR	181/660 (27.4)	NR
India (ref. *102*)	1976–85	Urban	87/1919 (4.5)	136/4050 (3.4)	86/983 (8.7)
Philippines (ref. *103*)	1982–88	Urban	24/110 (21.8)	91/306 (29.7)	31/93 (33.3)
Philippines (ref. *49*)	1983–84	Urban	21/346 (6.1) Median % 14.0[c]	53/674 (7.9) Median % 18.8[c]	NR
Median %			**13.5**	**15.6**	**18.5**

[a] When data were not stratified into these age categories, the results were assigned to the most comparable group.

[b] NR: not reported.

[c] A median was derived for the Philippines since both studies involved similar populations during overlapping times.

setting. The overall rate in 1996 was 5.6 per 100 000 population.

***Shigella* in France.** During the most recent 6-year period for which data are available (1992–97), an average of 962 cases of *Shigella* infection were reported to the *Centre National de Référence des Salmonella et Shigella*, Pasteur Institute, Paris. Applying the United Nations estimate of France's population in 1995 yields a rate of 1.8 cases per 100 000 population.

***Shigella* infection in England and Wales.** The age-specific incidence of shigellosis in England and Wales has been estimated for 1996, based on cases reported to the Public Health Laboratory Service. The incidence of *Shigella* infection was 3.3 cases per 100 000 population (Table 7).

***Shigella* infection in Israel.** During the most recent 5-year period for which data are available (1991–95), the mean incidence of laboratory-confirmed *Shigella* infection in the civilian population of Israel that was reported to regional health authorities was 130 cases per 100 000 population per year (*56*). Age-specific incidences for the Jewish and non-Jewish populations are shown in Table 7.

***Shigella* infection in the USA.** A total of 59 527 cases of laboratory-confirmed *Shigella* infection were reported to the US National Shigella Surveillance System (PHLIS) over the 5-year period 1990–94 (average 11 900 per year) (*55*). Over the same period, an additional 27 899 cases were reported from states not participating in the PHLIS system, yielding a total number of 87 426 *Shigella* cases for the USA, i.e. an average of 17 500 cases per year (*55*). This corresponds to 6.5 cases per 100 000 population (Table 8). The age-specific incidences of shigellosis, calculated from the reported age data of a single year (1 October 1994 to 12 September 1995), are shown in Table 7 (*55*).

***Age-specific and total burden of* Shigella *in industrialized countries*.** As shown in Table 7, the incidence of shigellosis reported in Australia, England and Wales, France, and the USA is similar, ranging from 1.8 to 6.5 cases per 100 000. The incidence reported from Israel is approximately 20-fold higher than that from the USA, which is consistent with previous observations (*11*); the high incidence in Israel is probably not representative of most industrialized countries and reflects the high endemicity of shigellosis in the Middle East (*11*).

These estimates do not take into account that surveillance data are notoriously fraught with underreporting, the magnitude of which is uncertain (*11, 57*). By comparing the known number of *Shigella* cases that occur during outbreaks with cases that actually get reported to the health department during the same outbreaks, the Centers for Disease Control and Prevention (CDC) estimates that only 1–5% of *Shigella* cases are reported, which suggests that the cases ascertained by the health authorities underestimate the true incidence by a factor of 20–100 (*57*).

The incidences of shigellosis in the USA were used to calculate the age-specific and total burden of shigellosis in industrialized countries for the following reasons: the data from the USA appear to be representative of other industrialized countries; the data are broken down by age; and a correction factor for underreporting is available. To account for underreporting, we multiplied the cases ascertained by health authorities by a correction factor of 20, yielding an overall incidence of 130 cases per 100 000. If the total population living in developed countries is

Table 7. **Age-specific annual incidence of shigellosis, by country, using cases reported to the national surveillance systems of several industrialized countries**

	Annual number of cases per 100 000 population per year					
		Israel[b]				
Age group	USA[a]	Jewish population	Non-Jewish population	England and Wales[c]	Australia[d]	France[e]
0–11 months	12.5	80	45	5.1	NR[f]	NR
1–4 years	35.0	425	75	7.3	NR	NR
5–14 years	13.0	200	25	8.3	NR	NR
15–59 years	3.7	NR	NR	6.3	NR	NR
>60 years	1.1	NR	NR	1.2	NR	NR
Overall	**6.5**	**130**		**3.3**	**5.6**	**1.8**

[a] Data for 1 October 1994 to 12 September 1995 (ref. *55*).

[b] Data for 1989–93 (ref. *56*).

[c] 1996 data from the Public Health Laboratory Service, Communicable Disease Surveillance Centre, London, England.

[d] Population-based incidences comes from all States and Territories except New South Wales, where reporting was limited to foodborne or institutional outbreaks.

[e] Surveillance based on cases reported to the Centre National de Référence des Salmonella et Shigella, Institut Pasteur, Paris, from 1992 to 1997.

[f] NR: not reported.

Table 8. **Estimate of the global *Shigella* disease burden**

Age group (years)	No. of cases		
	Developing countries	Industrialized countries[a]	Total
0–4	113 163 260[b]	467 410	113 630 670
5–14	14 654 230[c]	408 875	15 063 105
15–59	30 065 470[c]	528 655	30 594 125
⩾60	5 296 565[c]	46 915	5 343 480
Overall	**163 179 525[c]**	**1 516 575**	**164 631 380**

[a] Calculated by multiplying the population of industrialized countries falling into each age group (ref. *35*) by the age-specific incidence of shigellosis in the USA (Table 7) (ref. *55*) and applying a correction factor of 20 to compensate for underreporting (ref. *57*).

[b] From Table 4.

[c] From Table 5.

1150 million, each year 1.5 million persons experience an episode of shigellosis.

Global burden of shigellosis. The total number of *Shigella* episodes that occur each year throughout the world is estimated to be 164.7 million, i.e. 163.2 million cases in developing countries and 1.5 million cases in industrialized countries (Table 8).

Mortality from shigellosis in developing countries

Mortality in developing countries among infants and 0–4-year-olds. An estimate of *Shigella*-associated mortality among 0–4-year-olds can be derived using the equations devised to calculate disease burden (Tables 1–6). The results of this strategy are depicted in Table 9. Mortality rates observed among patients admitted to the inpatient unit of the International Center for Diarrheal Diseases Research, Bangladesh (ICDDR, B) over the period 1974–88 were used for these calculations (*6*). Estimations indicate that 13.9% of infants and 9.4% of 1–4-year-olds who are hospitalized with shigellosis die each year; the total numbers of deaths in these age groups are therefore 66 070 and 29 315, respectively (Table 9).

Studies performed in the 1980s in both rural and urban settings have provided evidence that many additional diarrhoeal deaths occur at home for reasons that include family preference, access to care, and long-term complications of the illness. A one-year census-based survey of deaths among children younger than 7 years in a rural area of the Gambia found that only 12% of deaths occurred in a hospital or health centre (*58*). Only 17.8% of deaths detected during the 3 months following admission for shigellosis to the rural Diarrhoea Treatment Centre in Matlab, Bangladesh, occurred in the treatment centre (*6*). The mortality rate among 2–5-year-old children who had received medical treatment for diarrhoea during the preceding 4 months was slightly lower among those residing in urban Bangladesh than in the Gambia; however, the Bangladeshi study evaluated outpatients who were presumably less severely ill (*59*). These studies indicate that the true death rate may be 6–8-fold higher than that indicated by hospital records (*6, 58*). Multiplying the in-hospital mortality by a factor of 7 raises the death toll for infants to 462 490. A similar calculation for 1–4-year-old children yields 205 205 deaths, making a total of 425 810 deaths from *Shigella* infection among children aged 0–4 years living in developing countries (Table 9).

Older children and adults. Each year approximately 6 744 075 episodes of shigellosis among older children and adults living in developing countries are evaluated in treatment centres (Table 5). It is estimated that 11% of outpatients with *Shigella* infection are admitted to a hospital, i.e. 741 850 cases (*60*). At the ICDDR, B over the period 1974–88, 8.2% of patients older than 5 years who were hospitalized with *Shigella* infection died in the hospital (*60*), making 60 830 deaths each year for this age group. A correction for out-of-hospital deaths, similar to that used for children younger than 5 years of age, results in an estimated 425 810 *Shigella* deaths among older children and adults living in developing countries (*6, 58*).

Total mortality from shigellosis among persons residing in developing countries. Combining the mortality calculated for all age groups, we estimate the total *Shigella*-related mortality among persons living in developing countries to be 1 093 505 (Table 9). In this estimate, children younger than 5 years are responsible for 61% of all *Shigella*-related deaths (*61*).

Table 9. **Estimated annual mortality from shigellosis in developing countries, by age group**

	0–11 months	1–4 years	⩾5 years
No. of hospitalized cases that are infected with *Shigella* spp.[a]	475 315	311 850	741 850[b]
No. of hospitalized shigellosis cases that die (%)	66 070 (13.9)[c]	29 315 (9.4)[c]	60 830 (8.2)[d]
No. of shigellosis cases that die, corrected for out-of-hospital mortality[e]	462 490	205 205	425 810
Total *Shigella* deaths		**1 093 505**	

[a] From Table 4.

[b] Each year approximately 6 744 075 episodes of shigellosis among older children and adults living in developing countries are evaluated in treatment centres (Table 5), of whom an estimated 11% (741 850) are admitted to the hospital (ref. *60*).

[c] From ref. *6*.

[d] From ref. *60*.

[e] Because many deaths occur at home, it has been suggested that the true death rate may be 7-fold higher than indicated by hospital records (ref. *6*, *58*).

Mortality from shigellosis in industrialized countries

The death rate due to *Shigella* in developed countries is exceedingly low. For example, the case-fatality rate

during the 1980s was reported to be 0.4% in the USA (*62*) and 0.05% in Israel (*56*), with an average of 0.2%. This means that approximately 3030 of the 1 516 575 cases of shigellosis that occur in industrialized countries each year (Table 8) have a fatal outcome.

Shigellosis in high-risk populations

Although *Shigella* is endemic worldwide, it affects certain populations more than others. In developing countries, high rates of morbidity and mortality are known to occur among displaced populations. Using the USA as an example, identified risk groups in industrialized countries include children in day-care centres, native Americans on reservations, patients in custodial institutions, and homosexual men, which together account for approximately 13% of reported isolates; international travellers and their household contacts are responsible for an additional 20% (*62*).

Displaced populations. Sudden mass displacement of people as a result of war, famine, and ethnic persecution often results in large populations who face insufficient supplies of clean water, poor sanitation, overcrowding, and concomitant malnutrition (*63*). In this setting, epidemics of dysentery have caused high rates of morbidity and mortality among all age groups in several populations recently, including Bhutanese and Kurdish displaced populations in 1991 (*64*), Somalis in 1992 (*63*), Burundians in 1993 (*65*), and Rwandans in 1994 (*66– 68*). Dysentery produced extreme devastation among the 500 000–800 000 Rwandan refugees who fled into the North Kivu region of Zaire in 1994. During the first month alone, approximately 20 000 persons died from dysentery caused by a strain of *S. dysenteriae* type 1 that was resistant to all of the commonly used antibiotics (*66*).

Traveller's diarrhoea. In 1995, roughly 116 million persons travelled from industrialized to developing countries (personal communication, E. Paci, World Tourism Organization, 1995). Diarrhoea complicates approximately 50% of these trips (*69*), resulting in 58 million cases of illness. Black et al. reviewed all studies of traveller's diarrhoea conducted between 1974 and 1987 (*69*). In the 28 studies that attempted to identify cases of shigellosis, the median attack rate was 1% (range, 0–30%). If 50% of travellers develop diarrhoea and 1% is due to *Shigella*, then there are an estimated 580 000 cases of traveller's shigellosis among travellers from industrialized countries each year.

Travellers are infected with multiresistant *Shigella* with increasing frequency. In Helsinki, Finland, between 1975 and 1988, the National Shigella Reference Centre received 1951 *Shigella* isolates collected from travellers (*70*). Whereas 3% of strains were trimethoprim-resistant between 1975 and 1982, by 1988 a total of 98% were resistant. In the USA, fewer than 5% of domestically acquired *Shigella* isolates are resistant to trimethoprim–sulfamethoxazole, while about 10% are resistant to ampicillin (*62*). However, if there is a history of recent foreign travel by the patient or by a household member with diarrhoea, approximately 20% of isolates are resistant to trimethoprim–sulfamethoxazole and 60% are resistant to ampicillin (*62*).

Limited data on serotypes affecting travellers are available. Among 235 strains isolated from Japanese travellers, *S. sonnei* represented 64%, *S. flexneri* 25%, *S. boydii* 8%, and *S. dysenteriae* 3% (*71*). In national surveillance conducted in Finland between 1985 and 1988, 175 *Shigella* isolates were serotyped, yielding 71% *S. sonnei*, 25% *S. flexneri*, 3% *S. boydii*, and <1% *S. dysenteriae* (*70*).

Shigella *and the military*. Throughout history, bacillary dysentery among soldiers has played a decisive role in the course of military campaigns (*72*) and the risk continues in modern deployments. During Operation Desert Shield in the Arabian peninsula, 57% of US troops experienced an episode of diarrhoea and 20% reported that they were temporarily unable to carry out their duties because of diarrhoeal symptoms (*73*). *Shigella* was cultured from 26% of episodes (or 15% of all troops), as follows: *S. sonnei* (81%), *S. flexneri* (11%), *S. boydii* (7%), and *S. dysenteriae* (4%). Most (85%) of the *Shigella* strains tested were resistant to trimethoprim–sulfamethoxazole. In the course of Operation Restore Hope, during the famine and political unrest in Somalia, *Shigella* was identified in 37 (33%) of 113 diarrhoeal stools that were cultured from US soldiers: 23% were *S. sonnei*, 43% *S. flexneri*, 19% were *S. boydii*, and 15% were *S. dysenteriae* (*15*). A high level of resistance to doxycycline, ampicillin, and trimethoprim–sulfamethoxazole was reported.

Day-care centres. Shigellosis, particularly due to *S. sonnei*, has been associated with young children in schools and day-care centres from a number of industrialized countries (*13, 74–76*). This places a large proportion of young children at increased risk of infection. For example, in 1995 approximately 48% of the 65% of mothers in the USA who had children under 6 years of age and who were employed enrolled their children in family or centre-based day care (*77*). Thus 12.9 million children under 6 years of age are in day care with other children (*78*). It is well established that children enrolled in group care have a higher risk for shigellosis compared with age-matched controls living at home (*13, 79, 80*). During a community-wide outbreak of *S. sonnei*, children younger than 6 years who attended day care were 2.4 times more likely to experience shigellosis than were children who did not (*79*). When outbreaks occur in the day-care setting, attack rates are high (33–73%) (*81*) and secondary cases may be detected in 26–33% of the families of children who had *Shigella*-positive diarrhoea, confirming the important role of day-care centres in the dissemination of *Shigella* infection to the community (*13*, *82*).

Sensitivity analysis

We conducted a sensitivity analysis for disease burden and mortality. The best and worst case

scenarios were substituted for events for which a wide range of possible frequencies have been published. Outliers were excluded from range estimates, e.g. the percentage of *Shigella* diarrhoea episodes that received medical attention in Teknaf, Bangladesh, from Table 6 (*46*).

Burden of shigellosis. Ranges could be extrapolated from published studies for the incidence of diarrhoea in children from developing countries by age (*36*) and for the proportion of episodes attributed to *Shigella* (Tables 2, 3 and 6). Applying these ranges to the sensitivity analysis suggests that the number of episodes of shigellosis that occur each year in developing areas of the world may be as low as 80.5 million, or as high as 415.6 million (Table 10). For industrialized countries, we varied the assumed proportion of cases that are reported to national surveillance programmes from 10% (to derive a minimum estimate) to 1% (a maximum estimate if a correction factor of 100 were used, corresponding to the upper limit proposed by Eichner et al. (*57*)). This yielded a range of 750 000 to 7.5 million annual episodes of *Shigella* infection in the industrialized world. The worldwide burden is thus estimated to be between 81.3 million and 415.6 million episodes each year.

Mortality. Age-specific estimates of case fatality are sparse and most certainly vary widely, reflecting regional rates of factors such as malnutrition and access to medical care. For our estimates, we used the median mortality rates by age for patients infected with *Shigella* spp. who were admitted to the inpatient unit of ICDDR, B in Bangladesh during 1974–88 (Table 9), since these data were based on a prolonged observation interval, were systematically collected, and included 2–3 years in which *S. dysenteriae* type 1 was epidemic (*6*). Since the appropriate correction factor for out-of-hospital deaths is not known, we arbitrarily varied it from 4- to 10-fold. When these calculations were applied to the number of persons hospitalized with shigellosis derived from the sensitivity analysis, we estimated the annual death toll to range from 768 790 to 11 635 920 persons.

Global distribution of *Shigella* serogroups and serotypes

Distribution of serogroups. As shown in Fig. 1, the majority (median 60%, range 25–86%) of *Shigella* isolates from developing countries are *S. flexneri*, with *S. sonnei* being the next most common (median 15%, range 2–44%). *S. dysenteriae* (median 6%, range 1–31%) and *S. boydii* (median 6%, range 0–46%) occur equally frequently. *S. dysenteriae* is seen most often in South Asia and sub-Saharan Africa. In contrast, data from Israel, Spain, and the USA consistently demonstrate that *S. sonnei* is the most common serogroup found in industrialized countries (median 77%, range 74–89%), followed by *S. flexneri* (median 16%, range 10–21%), *S. boydii* (median 2%, range 2–5%) and finally *S. dysenteriae* (median 1%, range 0–1%).

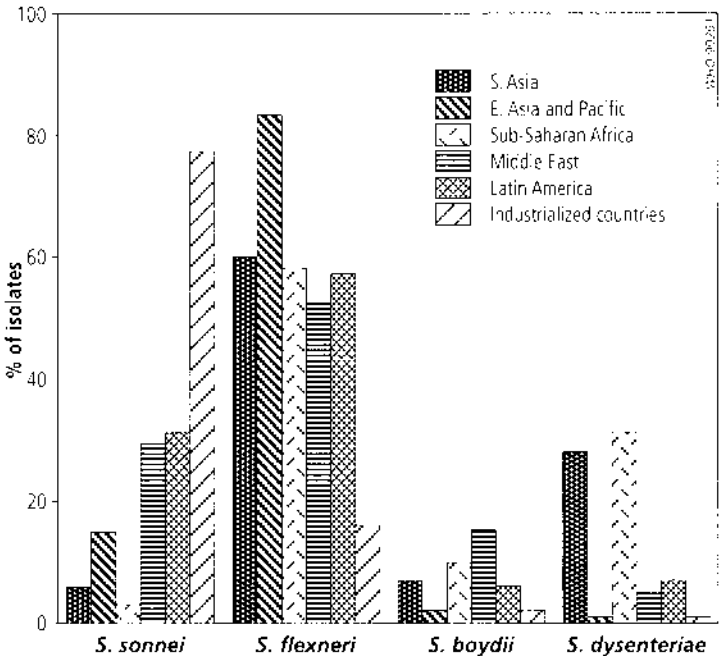
Distribution of serotypes. Among *S. flexneri* isolates from developing countries (Fig. 2), serotype 2a causes 32–58% of infections, followed by serotype 1b (12–33%), 3a (4–11%), and finally 4a (2–5%) and 6 (3–5%). In the USA, *S. flexneri* 2a and other

Table 10. **Sensitivity analysis of diarrhoeal disease burden and mortality in three settings in developing countries**

Age group	**0–11 months**		**1–4 years**		**5–14 years**		**15–59 years**		**>60 years**	
Total population	**125 000 000**		**450 000 000**		**1 011 000 000**		**2 647 000 000**		**330 000 000**	
Disease burden	Low	High	Low	High	Low	High	Low	High	Low	High
Diarrhoea episodes/person/year	2.7	5.0	1.7	3.0	0.65	0.65	0.5	0.5	0.69	0.69
Total diarrhoea (TD) episodes/year	337 500 000	625 000 000	765 000 000	1 350 000 000	657 140 250	657 140 000	1 323 304 000	1323 304 000	227 320 500	227 320 500
Diarrhoea episodes in domicile (DD)										
No. of episodes (% of TD)	297 675 000 (88)	551 250 000 (88)	703 035 000 (92)	1240 650 000 (92)	643 997 450 (98)	643 997 450 (98)	1296 837 920 (98)	1296 837 920 (98)	222 774 090 (98)	222 774 090 (98)
No. with *Shigella* (% of DD)	5 954 000 (2)	27 563 000 (5)	42 182 100 (6)	235 723 500 (19)	6 439 970 (1)	19 319 920 (3)	12 968 380 (1)	38 905 140 (3)	2 227 740 (1)	6 683 220 (3)
Diarrhoea episodes in outpatients (OD)										
No. of episodes (% of TD)	34 763 000 (10)	64 375 000 (10)	60 435 000 (8)	106 650 000 (8)	13 142 810 (2)	13 142 810 (2)	26 466 080 (2)	26 466 080 (2)	4 546 410 (2)	4 546 410 (2)
No. with *Shigella* (% of OD)	695 000 (2)	19 313 000 (30)	7 856 550 (13)	41 593 500 (39)	657 140 (5)	2 759 990 (21)	793 980 (3)	7 145 840 (27)	409 177 (9)	1 545 780 (34)
Diarrhoea episodes hospitalized (HD)										
No. of episodes (% of TD)	5 063 000 (2)	9 375 000 (2)	1 530 000 (0.2)	2 700 000 (0.2)						
No. with *Shigella* (% of HD)	203 000 (4)	1 031 000 (11)	122 400 (8)	864 000 (32)						
No. of *Shigella* episodes:										
Subtotal, by age strata	6 852 000	47 907 000	50 161 050	278 181 000	7 097 115	22 079 910	13 762 360	46 050 980	2 636 920	9 774 780
Subtotal, by age group		**Low:** 57 012 300	**High:** 326 087 250				**Low:** 23 496 390	**High:** 89 488 332		
Total annual *Shigella* episodes				**Low:** 80 508 690	**High:** 415 575 580					
Mortality	Low	High	Low	High	Low	High	Low	High	Low	High
Mortality from HD with *Shigella:*										
Uncorrected (% of HD)	28 150 (14)	143 340 (14)	11 510 (9)	81 220 (9)	53 890 (8)	226 320 (8)	65 110 (8)	585 960 (8)	33 553 (8)	126 750 (8)
Corrected for out-of-hospital mortality	112 600 (4x)	1433 440 (10x)	46 020 (4x)	812 160 (10x)	215 540 (4x)	2 263 190 (10x)	260 430 (4x)	5 859 590 (10x)	134 210 (4x)	1267 540 (10x)
Subtotal, by age group		**Low:** 158 610	**High:** 2 245 600				**Low:** 610 180	**High:** 9 390 320		
Total annual *Shigella* deaths				**Low:** 768 790	**High:** 11 635 920					

unspecified type 2 strains make up the largest component of *S. flexneri* isolates, followed by unspecified serotype 1 and 3. Among *S. dysenteriae* isolates, type 1 predominates in India, Nigeria, and Singapore (median for developing countries 30%, range 0–67%), while type 2 predominates in Guatemala, Hungary, and Yemen (median 23%, range 0–70% of *S. dysenteriae* isolates). The third most common serotype is type 3 (median 10%, range 0–20%). The remaining *S. dysenteriae* serotypes identified in developing countries are 4, 5, 6, 7, 9 and 10. The *S. dysenteriae* isolates from the USA are evenly distributed among types 1, 2 and 3. *S. boydii* serotype 14 predominates in India, Nigeria, and Yemen, where it accounts for 23–47% of isolates. *S. boydii* type 1 predominates in Singapore (44%) and serotype 2 in Guatemala (40%). In the USA, serotype 2 accounts for the largest proportion (42%) of *S. boydii* isolates.

Fig 1. **Percentage of *Shigella* isolates belonging to four serogroups, by region.** A median percentage was calculated for each region. When multiple studies were performed in one country, a median for each country was first calculated. The countries represented in each region were: South Asia (Bangladesh (5,44) and India (104)); East Asia and Pacific (Thailand (101, 105, 106), Malaysia (114) and Singapore (107)); sub-Saharan Africa (Nigeria (43, 108)); Middle East (Kuwait (109), Saudi Arabia (110, 111), Turkey (112) and Yemen (113)); Latin America (Chile (32) and Guatemala (34)); and industrialized countries (Spain (115), Israel (116–118) and USA (55)).



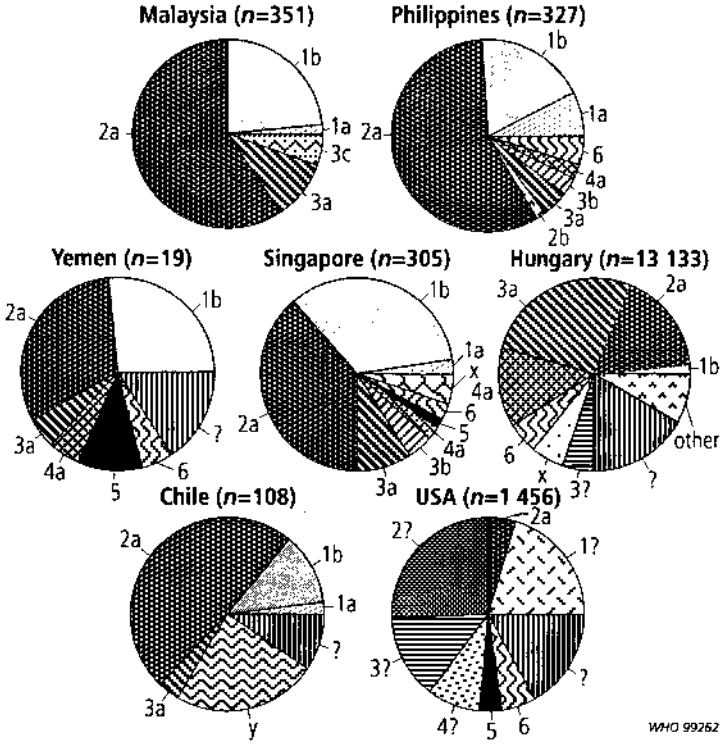
Discussion

Diarrhoeal disease continues to be a leading cause of morbidity and mortality worldwide, and is ranked fourth as a cause of death (*83*) and second as a cause of years of productive life lost due to premature mortality and disability *(84*). Even though economic development and progress in health care delivery are expected to catalyse substantial improvements in infectious-disease-related morbidity and mortality during the next 30 years, it is predicted that diarrhoea will remain a leading health problem (*85*). There has been increased recognition in recent years of the importance of *Shigella* as an enteric pathogen with global impact, and of the potentially devastating consequences if resistant strains outpace the availability of affordable and effective antimicrobial therapy. This awareness has led *Shigella* to be targeted by WHO as one of the enteric infections for which new vaccines are most needed and has prompted the present review, which estimates the global burden of *Shigella* disease.

We have estimated that each year 163.2 million episodes of endemic shigellosis occur in developing countries (3.5% of the population) and 1.5 million in industrialized countries (0.1% of the population). Approximately 1.1 million episodes (0.7%) result in death. Under-5-year-olds comprise the majority of cases (69%) and of fatal outcomes (61%). While death from *Shigella* infection is a rare outcome in industrialized countries, morbidity can be substantial when outbreaks of shigellosis occur in custodial institutions and day-care centres, and when shigellosis occurs among soldiers and travellers. It is interesting to compare our findings with other attempts to quantify the diarrhoeal disease burden. In 1984, an expert panel assembled by the Institute of Medicine estimated, on the basis of published studies and field experience, that the annual number of *Shigella* episodes in developing countries was 251 million, with 654 000 deaths. Extrapolation of these rates to the 1994 global population estimates would yield 324 million cases and 843 000 deaths (*54*), which is remarkably similar to our figures, considering the number of potential sources of error involved. Our findings can also be viewed in the context of an analysis performed by Bern et al. of the burden of diarrhoeal disease among young children living in developing countries. Based on published studies, Bern et al. estimated that, in 1990, children aged <5 years experienced approximately 1000 million episodes of diarrhoea per year, resulting in 3.3 million deaths (range 1.5–5.1 million) (*36*). Our findings, which are based in part on the incidence of diarrhoea among under-5-year-olds reported by Bern et al., are consistent with these estimates if *Shigella* causes 5–10% of diarrhoeal illnesses and 75% of diarrhoeal death (*6*).

It is difficult to derive a credible estimate of disease burden by compiling studies which vary in place, time, socioeconomic conditions, and study design, even if criteria for data inclusion are stringent. Nevertheless, there are many reasons to suspect that the potential sources of error have resulted in conservative estimates of disease burden. First, *Shigella* is a fastidious organism to cultivate under most field conditions, where prompt processing of fresh faecal material is not always possible; this would

Fig. 2. **Distribution of *Shigella flexneri* serotypes isolated in the following countries:** Malaysia (114), Philippines (103), Yemen (113), Singapore (107), Hungary (119), Chile (32), and USA (55). Only serotypes that constitute more than 1% of total *S. flexneri* isolates are shown.



falsely lower estimates of the proportion of diarrhoeal cases attributable to it. Second, the hospitalization rates for children aged <5 years (1.5% of diarrhoeal episodes) used in our calculations as a surrogate for severe disease may be low for developing countries because they were derived from surveillance conducted in Chile, a rapidly developing country with a strong health care infrastructure, little malnutrition, and almost no *S. dysenteriae* type 1 infections. In contrast, 10% of patients arriving with diarrhoea at the Diarrhoea Treatment Centre in Dhaka, Bangladesh, are admitted to a unit for inpatients (*6*). Third, it is likely that we have underestimated the incidence of diarrhoea among older children and adults living in developing countries (for whom the data are sparse); higher rates of diarrhoea and enteric illness have been reported among similarly aged populations living in the USA during the 1950s to 1970s (*86, 87*). Furthermore, population-based studies in the USA indicate that a physician is consulted for 15% of episodes of diarrhoeal illness (*86*), whereas we estimated that only 2% of older children and adults from developing countries seek medical care. Fourth, although the use of inpatient case-fatality rates derived from Dhaka (a highly underserved population) may produce overestimates of case fatality, our calculations did not fully account for the sudden excess of cases and deaths that occurs when epidemic waves of Shiga dysentery strike a region. This devastating form of shigellosis is associated with high rates of illness (attack rates have ranged from 1.2% in El Salvador to 32.9% during an outbreak on St Martin island) and case fatality (ranging from 0.6% during an epidemic in Myanmar (Burma) to 7.4% in the Guatemalan epidemic) (*6, 8 ,9, 68, 88, 89*). Finally, the available data only permit an estimation of deaths that occur during the acute or subacute phase of shigellosis. Deaths that result after extended periods of persistent diarrhoea, intestinal protein loss, and chronic malnutrition following shigellosis could not be measured.

A safe and effective *Shigella* vaccine offers great potential as a means of controlling shigellosis. The ability of *Shigella* antigens to confer a high degree of serotype-specific immunity has been observed in several situations, e.g. large-scale field trials with the streptomycin-dependent vaccines of Mel et al. (*90, 91*), studies of volunteers who were inoculated with either the vaccine or wild-type *Shigella* and then challenged with the homologous virulent serotype (*92– 94*), and natural history studies in Chile (*32*). However, protection across the four species (*S. dysenteriae, S. flexneri*, S. *boydii*, and *S. sonnei*, also designated as groups A, B, C and D, respectively) does not occur (*95*).

Strategies for vaccine development must take into consideration the 47 antigenically distinct serotypes of *Shigella*. Groups A, B, and C contain multiple serotypes (13, 6 (15 including subtypes), and 18, respectively), whereas group D contains only a single serotype. Our analysis highlights the *Shigella* strains that are most critical and which should be included in a potential vaccine. *S. sonnei* is an essential vaccine component since it is responsible for 15% of infections in developing countries and 77% in industrialized countries. *S. dysenteriae* comprises only a small proportion of the overall burden from endemic disease (median, 6% in developing countries and 1% in industrialized countries). However, the severe manifestations characteristic of serotype 1, which comprised about 30% of *S. dysenteriae* isolates, and its ability to cause pandemic spread, harbour multiple antibiotic resistances, and produce high attack rates and case fatality in all age groups, argue for its inclusion in a polyvalent formulation. The presence of 15 serotypes of *S. flexneri* presents a logistic barrier for vaccine development. There is evidence of serologic cross-reactivity in humans (*96*) and of cross-protection among the *S. flexneri* serotypes in animals (*97*), suggesting that broad *S. flexneri* protection may be feasible with the use of innovative strategies. If a polyvalent vaccine cocktail could be developed that covers 100% of *S. flexneri* strains, the addition of *S. sonnei* and *S. dysenteriae* type 1 could provide protection against an estimated 79% of *Shigella* infections in developing countries and 83% in industrialized countries. If this vaccine had 70% efficacy and the coverage was high, up to 91 million infections (90.2 million in developing countries and 881 130 in industrialized countries) and 605 000 deaths might be prevented each year. ■

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Résumé

Charge de morbidité des infections à *Shigella* dans le monde : incidence sur la mise au point et l'utilisation des vaccins

Peu de publications fournissent les données nécessaires pour pouvoir estimer la morbidité et la mortalité associées aux infections à *Shigella* dans le monde. De telles estimations sont pourtant importantes, puisqu'on en a besoin pour planifier les programmes de mise au point et d'utilisation des vaccins et autres stratégies de lutte.

Nous avons passé en revue la littérature scientifique publiée entre 1966 et 1997 afin d'obtenir des données permettant de calculer le nombre de cas d'infections à *Shigella* et la mortalité qui leur est associée chaque année dans le monde. La charge de morbidité a été déterminée séparément pour les pays en développement et les pays industrialisés, par groupe d'âge (0–11 mois, 1–4 ans, 5–14 ans, 15–59 ans et $\geqslant$60 ans) et, à titre d'indicateur de gravité de la maladie, par catégorie clinique (cas bénins soignés à domicile, cas plus graves ayant nécessité des soins cliniques dans un centre de traitement mais sans hospitalisation, et cas ayant nécessité une hospitalisation). On a effectué une analyse de sensibilité pour pouvoir estimer les valeurs supérieures et inférieures de la morbidité et de la mortalité dans chaque catégorie. Enfin, on a déterminé la distribution de fréquence des infections à *Shigella* par sérogroupe et par sérotype pour les différentes régions du monde.

Le nombre annuel d'épisodes de diarrhée à *Shigella* se produisant dans le monde a été estimé à 164,7 millions, dont 163,2 millions dans les pays en développement (fourchette 80,5–415,6 millions) et 1,5 million dans les pays industrialisés (fourchette 0,8–7,5 millions). On estime à 1,3 million (fourchette 0,3–4,9 millions) la mortalité totale associée aux infections à *Shigella* chez les personnes vivant dans les pays en développement. Dans ces estimations, les enfants de moins de 5 ans représentent 69% de tous les épisodes et 61% de tous les décès imputables à la shigellose. Les pourcentages médians des isolements de *Shigella* ont été les suivants : *S. flexneri* (60%), *S. sonnei* (15%), *S. boydii* (6%) et *S. dysenteriae* (6% : dont 30% sont des isolements de *S. dysenteriae* type 1) dans les pays en développement; et elle a été respectivement de 16%, 77%, 2% et 1% dans les pays industrialisés. Dans les pays en développement, les sérotypes de *S. flexneri* qui prédominent sont le 2a (32–58%), suivi du 1b (12–33%), du 3a (4–11%), et enfin du 4a (2–5%) et du 6 (3–5%). Dans les pays industrialisés, la plupart des isolements appartiennent au sérotype 2a de *S. flexneri* ou à d'autres souches de type 2 non spécifiées. Les shigelles jouent régulièrement un rôle important comme germes entéropathogènes ayant un impact mondial, que les mesures de prévention et de traitement existantes ne permettent pas de maîtriser suffisamment. Des stratégies novatrices visant à mettre au point un vaccin permettant de couvrir les sérotypes les plus répandus pourraient offrir bien des avantages.

Resumen

Carga mundial de infecciones por *Shigella* : implicaciones para el desarrollo y empleo de vacunas

Pocas son las publicaciones que facilitan los datos necesarios para estimar la morbilidad y mortalidad mundiales asociadas a las infecciones por *Shigella*. Sin embargo, esas estimaciones son importantes, dada su necesidad para establecer programas de desarrollo y empleo de vacunas y otras estrategias de control.

Examinamos la literatura científica publicada entre 1966 y 1997 para obtener datos a fin de calcular el número de casos de *Shigella* que se producen cada año en todo el mundo y la consiguiente mortalidad. Se determinó, por separado, la carga de la enfermedad para los países en desarrollo y para los industrializados, por estratos de edad (0-11 meses, 1-4 años, 5-14 años, 15-59 años y $\geqslant$60 años) y, como indicador de la gravedad de la enfermedad, por categorías clínicas (casos leves que permanecen en casa, casos más graves que necesitan atención clínica en un centro de tratamiento pero que no requieren hospitalización, y casos que exigen hospitalización). Se realizó un análisis de sensibilidad para estimar los valores máximo y mínimo de la morbilidad y la mortalidad en cada categoría. Finalmente, se determinó la distribución de frecuencias de la infección por *Shigella* por serogrupo y serotipo y por región del mundo.

El número anual de episodios de infección por *Shigella* que se producen en todo el mundo se estima en 164,7 millones, que incluyen 163,2 millones de casos en los países en desarrollo (intervalo 80,5-415,6 millones) y 1,5 millones de casos en los países industrializados (intervalo 0,8-7,5 millones). La mortalidad total asociada a *Shigella* entre las personas que habitan en los países en desarrollo se estima en 1,3 millones (intervalo 0,3-4,9 millones). En estas estimaciones, los niños menores de cinco años representan el 69% de todos los episodios y el 61% de todas las defunciones atribuibles a shigelosis. La proporción mediana de aislamientos de *Shigella* fue la siguiente: *S. flexneri* (60%), *S. sonnei* (15%), *S. boydii* (6%) y *S. dysenteriae* (6%: un 30% de los cuales

corresponden a *S. dysenteriae* tipo 1) en los países en desarrollo; y 16%, 77%, 2% y 1% respectivamente en los países industrializados. En los países en desarrollo los serotipos de *S. flexneri* predominantes son 2a (32%-58%), seguido de 1b (12%-33%), 3a (4%-11%) y, por último, 4a (2%-5%) y 6 (3%-5%). En los países industrializados la mayoría de los aislamientos corresponden a *S. flexneri* 2a o a otras cepas del tipo 2 no especificadas. *Shigella* tiene grandes repercusiones como patógeno entérico a nivel mundial, y no puede controlarse correctamente con las medidas de prevención y tratamiento existentes. La aplicación de estrategias innovadoras con miras al desarrollo de una vacuna que abarque los serotipos más comunes podría aportar beneficios sustanciales.

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